

Reference	Sample	Inclusion criteria	Results of autonomic function: COPD versus CON	Influencing factors (COPD): significant (*) relationship/association exist between;
Antonelli Incalzi et al, 2009 ²⁶	54 COPD (46♂, 8♀)69.1±7.7yr 95 CON (80♂, 15♀): 68.8±9.0yr	COPD&CON: diagnosis of COPD according to ATS, undergoing in hospital rehabilitation following non smokers COPD and CON: Randomly assigned		LF/HFnu* and disease severity, PaCO ₂ , FEV ₁ , loss of IADL, functional status Circadian rhythm and VLFP, LFnu, HFnu and LF/HFnu*,
Bartels et al, 2012 ¹¹	14 ♀COPD :62±8yr 14 ♀CON :59±6yr	COPD: COPD, on b agonist medication CON: Healthy, No medication COPD and CON matched: post- menopausal, ex-smokers Nil cardiac disease	BRS ↓ (p<0.001)	
Bedard et al, 2010 ⁴¹	41 COPD: (28♂, 13♀) 67±7yr 19 CON: (14♂, 5♀) 68±7yr	COPD: Clinically stable (GOLD), on medication CON: Healthy COPD and CON matched: Age sex and smoking	NN= PNN50= RMSSD = SDANN= SDNN = LF= HF= LF/HF ↓	LF/HF ratio and FEV ₁ * (r=0.342) and Age* (r=0.342)
Barnerdi et al, 2008 ²⁷	15 COPD: (10♂, 5♀)62±8yr 28 CON: (13♂, 15♀)59±6yr	COPD: Mild (GOLD), on medication CON: Healthy COPD and CON matched: , smokers, Non/never-smokers	BRS ↓ (p<0.001)	
Bir et al, 2005 ¹⁷	30 COPD: (21♂, 9♀)60.9±9.5yr 21 CON: (15♂, 6♀)57.3±7.9yr	COPD: Mild to severe (GOLD), no medication, ex-smoker CON: Healthy, Non-smokers COPD and CON matched:	SSR ↓ (p<0.05)	SSR* and FEV ₁ /FVC and % FEV ₁ /FVC
Borghesi-Silva et al, 2008 ³⁹	19♂ COPD69±8yr 8 ♂ CON 68±5yr	COPD: FEV ₁ <50% predicted, no medication, ex-smoker CON: Healthy, Non-smokers COPD and CON matched: Sedentary, Nil other chronic diseases	RMSSD ↓ SDNN ↓ LF ↓ HF= LF/HF ↓ LFnu ↓ HFnu ↑ (p<0.05)	
Cammilo et al, 2008 ¹	31 COPD(16♂, 15♀)66±8yr	COPD: COPD(GOLD), no medication		SDNN* and ADL, total daily energy expenditure, BMI, FFM, triceps and quadriceps muscle force, daily expenditure and number of steps >3METs, time spent in ADL >3METs and LCADL. SDNN index* and energy expenditure LF/HF ratio* and total daily expenditure, FFM, triceps and quadriceps muscle force R-R interval*time spent walking and standing, BMI, QOL No relationship between PFT, Fat mass and HRV No relationship between QOL and SDNN, LF/HF
Cammilo et al, 2011 ²	40 COPD (21♂, 19♀) COPD:67±7yr CON: 65±10yr	COPD: GOLD 2-3, CON: GOLD 2-3, COPD and CON matched: regular PA, no unstable cardiac dx, no comorbidity, randomly assigned		Time spent walking and HRV* Biceps and triceps muscle force and SDNN* No relationship between QOL and HRV No relationship between smoking status and RMSSD Dyspnea and RMSSD*
Carvalho et al, 2011 ³	15 COPD(9♂, 6♀)73.9±6.6yr: 15CON(8♂, 7♀) 68.7±7.3yr	COPD: Diagnosis of COPD (GOLD), excluded smokers, recent exacerbation, no medication CON: Healthy (normal lung function) COPD and CON matched:	RMSSD ↓ SDNN ↓ LF ↓ HF ↓ (p<0.05)	
Chang et al, 2011 ²⁸	9 COPD(not stated)	COPD: GOLD 2-3 Bronchodilators stop before testing, excluded unstable cardiac /musculoskeletal dx and patients on active phase pulmonary rehab		Respiratory rate and LF and HF* Ventilatory effort and LF and HF*
Chen, Chen & Kuo et al, 2006 ³⁴	30 COPD: (25♂, 5♀) 69.6±8.5yr 18 CON: (15♂, 3♀) 64.6±9.0yr	COPD: Moderate to severe (GOLD) Bronchodilators stop before testing CON: Healthy Excluded those with unstable cardiac COPD and CON matched: Age	SDRR ↓ CVRR ↓ TP ↓ LF ↓ HF ↓ LF/HF= LFnu= HFnu= (p<0.001)	No relationship between FEV ₁ % Predicted and FEV ₁ /FVC ratio vs HFnu and LF/HF ratio PaO ₂ and LF, HF and LF/HF*
Chhabra & De, 2005 ³⁷	56♂COPD57.96±9.8 1yr 11♂ CON: 50.82±9.82yr	COPD: diagnosis of COPD by BTS, history of >20 pack-years of cigarette smoking, no recent exacerbation, no metabolic dx CON: Healthy, non- smokers COPD and CON: Age matched	Valsalva ratio ↓ (p<0.01) ΔIE: ↓ (p<0.05) 30:15 ratio ↓ (p<0.05)	Disease severity and% FEV ₁ * PaO ₂ and valsalva ratio and 30:15 ratio* No relationship between PaO ₂ and PaCO ₂ and HRV TLCO ₂ and 30:15 ratio* MPAP and valsalva ratio*
Costes et al, 2004 ¹⁰	21 COPD: (♂, ♀) 62±9yr 18 CON: (♂, ♀)	COPD: GOLD 1-2, on medication CON: Healthy COPD and CON matched: , Age,	BRS ↓ (p<0.05) LF= HF=	No relationship between FEV ₁ , % FEV ₁ , FVC, %FVC, RV, FEV ₁ /FVC, PaO ₂ with BRS

	66±1yr		LFnu= HFnu= (p>0.05)	
Dias de Carvalho et al, 2011 ¹³	17 COPD(10♂, 7♀)73.1±5.6yr 17 CON: (8♂, 9♀): 68.8±8.6yr	COPD: diagnosis of COPD by LF (GOLD 2-3), excluded smokers, recent exacerbation, no medication/metabolic dx CON: Healthy (normal LF) COPD and CON: matched	SD1 ↓ SD2 ↓ TINN ↓ RRTri ↓ (p<0.05)	
Fatouleh, Vaughan &Macefield, 2011 ³²	15 COPD: (8♂, 7♀)71±2yr 12 CON ₁ : (8♂, 4♀)29±2yr 13 HTN: (10♂, 3♀)53±2yr 10 CON ₂ : (5♂, 5♀) 50±3yr	COPD: diagnosis of COPD, on medication 12 CON ₁ : Healthy 13 HTN: on their regular medication 10 CON ₂ : Healthy	MSNA ↑ (both burst frequencies and burst incidence) p<0.05	
Gunduz et al, 2011 ³⁵	25 COPD: (22♂, 3♀)63±7yr 25 CON: (19♂, 6♀) 60±8yr	COPD: stable, ambulatory, GOLD 2-3 CON: Healthy COPD and CON matched: AGE	sNN50 ↓ (p<0.05) pNN50 ↓ (p<0.05) SDNN ↓ (p<0.001) SDNNi ↓ (p<0.01) SDANN ↓ (p<0.01) RMSSD ↓ (p<0.01)	
Haidar et al, 2009 ¹⁹	18 COPD(10♂, 8♀) 51.7±2.4yr 14 CON: (5♂, 9♀): 47.7±2.8yr	COPD: GOLD 1-2, no medication, ex-smoker Placebo: GOLD 1-2, no medication, ex-smoker CON: Healthy, Non-smokers COPD, Placebo and CON matched: Age	BRS ↓ (p<0.025) RRi ↓ (p<0.05)	FEV ₁ and FEV ₁ /FVC and BRS* FEV ₁ and FEV ₁ /FVC and R-R interval*
Lewis, Annadale & Lewis, 2009 ⁷	10 COPD: (7♂, 3♀)73.9±7.2yr	COPD: STAGE 3-4 (GOLD), Excluded patients on beta blockers and other drugs affecting ANS		Circadian rhythm (morning time)vs HRV (QT multi-fractality, R-R & QTV index)*
Ramos et al, 2009 ²⁹	16 COPD(12♂,4♀): 64±11yr	COPD: COPD(GOLD 1-3), mean FEV ₁ 60±25% of predicted, no medication, no ANS associated diseases		No correlation was found between severity and RMSSD
Raupach et al, 2008 ³¹	15 COPD(11♂, 4♀) 60.9±1.4yr 15 CON:(11♂, 4♀) 60.7±1.4yr	COPD: FEV ₁ ≤60% predicted (GOLD), no diuretic medication Between 30-80 years CON: Healthy COPD and CON matched: Nonsmoking, age, weight & sex	BRS ↓ (p=0.009) MSNA ↑ (p<0.001)	Respiratory rate and BRS * and MSNA*
Raupach et al, 2011 ³³	15 COPD(11♂, 4♀) 60.9±1.4yr 15 CON:(11♂, 4♀) 60.7±1.4yr	COPD: FEV ₁ ≤60% predicted (GOLD), no diuretic medication Between 30-80 years CON: Healthy COPD and CON matched: Nonsmoking, age, weight & sex	MSNA↑ (burst incidence) (p<0.013)	
Reis et al, 2010 ³⁶	10 ♂ COPD69±9yr 9 ♂ CON:64±5yr	COPD: FEV ₁ ≤60% predicted (GOLD), FEV/FVC <0.7 stable clinically, on normal medication, nonsmoker CON: Healthy, no cardiac & metabolic dx COPD and CON matched: LFT, FC	LF↓ HF= SDNN= RMSSD= (p<0.05)	MIP and ΔIE *
Reis et al, 2010 ³⁸	10 ♂ COPD: 69±9yr 9 ♂ CON:64±5yr	COPD: FEV ₁ ≤60% predicted (GOLD), FEV/FVC <0.7 stable clinically, on normal medication, nonsmoker CON: Healthy, no cardiac & metabolic dx COPD and CON matched: LFT, FC	RRi = SDNN ↓ RMSSD ↓ LF ↓ HF ↓ LFnu= HFnu= LF/HF = (p<0.05)	
Sin et al, 2007 ⁴⁶	21COPD(10♂,11♀) COPD:64.1±9.7yr CON: 66.6±10.6yr	COPD and CON: clinical diagnosis of COPD,≥10 pack/yr smoking history, FEV ₁ <70% predicted, excluded cardiac dx coexisting disorder, cognitive impairment, poor prognosis		Circadian rhythm (Night time)and SDNN* and SDANN*
Suh et al 2013 ⁶	30 COPD(15♂, 15♀) 59.1±11.2yr 30 CON (15♂, 15♀) 59.2±11.3yr	COPD: FEV ₁ ≤60% predicted (GOLD), FEV/FVC <0.7 anxious and non-anxious CON: Healthy, anxious and non-anxious COPD and CON matched: Age, sex		Anxiety and SDNN and HF*
Tug et al 2005 ⁴⁵	35 COPD(15♂, 15♀) 65.2±7.29yr 15♂CON 56.24±7.69yr	COPD: According to GOLD criteria, excluded those on drugs affecting the ANS, other chronic comorbidities CON: Healthy, COPD and CON matched: Age		No correlation was found between severity age, smoking status, PaO ₂ , SaO ₂ age of illness and SSR (p>0.05) No correlation was found between severity age, smoking status, PaO ₂ , SaO ₂ age of illness and RRi (p>0.05)
van Gestel et al, 2011 ³	60COPD (23♂,37♀)65.2±7.7y r	COPD: diagnosed GOLD I-IV, clinically stable, 40-75years, FEV ₁ <80% predicted, normal BMI , excluded; CVD dx cancer, other respiratory dx, history of lung surgery, unable to ambulate, receiving corticosteroids other vasoactive medication		HRQOL and RMSSD, HF, LF/HF ratio*
van Gestel et al, 2012 ⁸	154 COPD (67♂,87♀) 62.5±10.7yr	COPD: diagnosed based on GOLD guidelines. clinically stable, 40-75years, patients on long term corticosteroids or morphine medications, mental or physical disability, acute or recent exacerbation		Exercise capacity (6MWT) and physical activity with HRV (NNmean)*

		(6 weeks).		
Yazici et al, 2007 ³⁰	28COPD(♂,♀) 64±10yr	COPD: clinical diagnosis COPD (ATS/ERS) with HRF and excluded those with cardiovascular diseases, diabetes, disease, hemodynamic instability, systemic disorders that can affect ANS		No significant relationship between PaO ₂ , PH and PaCO ₂ and HRV
Zamarron et al, 2014 ⁴⁰	23 ♂ COPD 69.6±7.3yr 8 ♂ CON: 68.6±4.9yr	COPD: According to GOLD criteria, BMI: 28.7±5.4kg/m ² , treated with b-agonists and anti cholinergics, sever but stable condition, CON: Healthy, BMI: 28.2±3.8kg/m ²	HF ↑ LF ↑ LF/HF ratio = TP= (p<0.05; p<0.01)	HRV(POW) and peak flow * Acute exacerbations and LF, HF and POW *.

Table 1: Evidence table of included studies

KEY: COPD: chronic obstructive pulmonary disease, CON: control, *: significant relationship, ↓: significantly lower in COPD, ↑: significantly higher in COPD, =: no significant difference; p: alpha probability level, ♂: male, ♀: female, vs: versus, GOLD: Global initiative for obstructive lung disease, LF: lung function, FEV₁: forced expiratory volume in one second, FVC: forced vital capacity, MET: metabolic equivalence, BRS: baro receptor sensitivity, MSNA muscle sympathetic nerve activity, SSR: sympathetic skin response, HRV: heart rate variability, RMSSD: square root of the mean of the sum of the squares of differences, RRi: RR waves interval, SDANN: standard deviation of the averages of NN intervals in all 5-minute segments of the entire recording, SDNN: standard deviations of all NN intervals, sNN50: total number of differences between adjacent RR intervals that were greater than 50ms, 30:15 ratio: the ratio between the shortest R-R interval around the 15th beat and longest R-R interval around the 30th beat, I-E difference/ ΔIE: difference of heart rate during inspiration and expiration, RRtri: variability triangular index, TINN: triangular interpolation of RR interval, SD1: standard deviation of instantaneous beat-to-beat variability, SD2: standard deviation in long term of the RR interval, SDRR: standard deviation of RR interval, CVRR: coefficient of variation of RR interval, TP: total power, HF: high frequency, VLF: very low frequency, LF: low frequency LF/HF: low-high frequency ratio. ADL: activity of daily living, nu: normalized, ab: absolute, ATS: Ameican thoracic society, TP: total HRV power.

Table 2: Table of evidence synthesis

S/ No	Author and year	1	2	3	4	5	6	7	Total (P-C)				Meth. Qual. (%)	Evid. grade
1	Bartels et al, 2012 ¹¹	+	+	+	+	-	+	+	6/7				86	B
2	Bedard et al, 2010 ⁴¹	+	+	+	+	-	+	+	6/7				86	B
3	Bernadi et al, 2008 ²⁷	+	+	-	+	-	-	+	4/7				57	B
4	Bir et al, 2005 ¹⁷	+	+	+	+	-	+	+	6/7				86	B
5	Borghi-Silva et al, 2008 ³⁹	+	+	+	+	-	+	+	6/7				86	B
6	Carvalho et al, 2011 ³	+	+	-	+	-	+	+	5/7				71	B
7	Chen, Chen &Kuo, 2006 ³⁴	+	+	-	+	-	+	+	5/7				71	B
8	Chhabra& De, 2005 ³⁷	+	+	-	+	-	+	+	5/7				71	B
9	Costes et al, 2004 ¹⁰	+	+	-	+	-	-	+	4/7				57	B
10	Dias de Carvalho et al, 2011 ¹³	+	+	+	+	-	+	+	6/7				86	B
11	Fatouleh, Vaughan &Macefield, 2011 ³²	+	+	-	+	-	+	+	5/7				71	B
12	Gunduz et al, 2009 ³⁵	+	+	-	+	-	+	+	5/7				71	B
13	Raupach et al, 2008 ³¹	+	+	+	+	-	+	+	6/7				86	B
14	Raupach et al, 2010 ³³	+	+	+	+	-	+	+	6/7				86	B
15	Reis et al, 2010 ³⁶	+	+	-	+	-	+	+	5/7				71	B
16	Reis et al, 2010 ³⁸	+	+	-	+	-	+	+	5/7				71	B
17	Suh et al, 2013 ⁶	+	+	+	+	-	+	+	6/7				86	B
18	Tug, Terzi &Yoldas 2005 ⁴⁵	+	+	+	+	-	+	+	6/7				86	B
19	van Gestel et al, 2012 ⁸	+	+	+	+	-	+	+	6/7				86	B
20	Zamarron et al 2014 ⁴⁰	+	+	+	+	-	+	+	6/7				86	B
	Author and year	1	2	3	4	5	6	7	8	9	Cohort			
21	Camillo et al, 2008 ¹	+	+	+	+	-	+	-	+	+	7/9		78	B
22	Camillo et al, 2011 ²	+	+	+	+	-	+	+	-	+	7/9		78	B
23	Chang et al, 2011 ²⁸	+	-	+	+	-	+	-	-	+	5/9		56	B
24	Lewis, Annandale and Lewis, 2009 ⁴	+	+	-	+	-	+	-	+	+	6/9		67	B
25	Ramos et al, 2009 ²⁹	-	-	+	+	-	+	-	-	+	4/9		45	B
26	van Gestel et al, 2011 ⁵	+	+	+	+	-	+	-	-	+	6/9		67	B
27	Yazici et al, 2007 ³⁰	+	+	+	+	-	+	-	+	+	5/9		56	
	Author and year	1	2	3	4	5	6	7	8	9	10	RCT		
28	Antonelli Incalzi et al, 2009 ²⁶	+	-	-	-	-	+	+	+	-	-	4/10	40	A2
29	Haidar et al 2009 ¹⁹	+	+	+	+	-	+	+	+	-	+	8/10	80	A2
30	Sin et al, 2007 ⁴⁶	+	+	-	+	-	+	+	+	+	+	8/10	80	A2

KEY: + : Agree and - : disagree, **For patient controlled studies**, 1: clear description of the patient group, 2: clear description of the control group, 3: well defined in/exclusion criteria, 4:clearly defined and appropriate intervention, 5 blinding, 6 identification of confounders in the design and analysis and 7: whether we considered the results valid and applicable. **For cohort studies**, 1:description of the patient groups, 2:selection bias excluded, 3: description of exposure and adequate evaluation, 4: description of outcome and adequate evaluation, 5:blinding, 6: Sufficiently long follow up (including drop-outs and loss on follow-up), 7:selective loss to follow up sufficiently excluded, 8: identification of confounders and 9: whether we considered the results valid and applicable. **While for RCTs**, 1: randomization, blinding of randomization, 3: patients blinded to treatment, 4: health care professionals blinded to treatment 5 Outcome assessors blinded to treatment, 6: groups comparable at baseline, 7 sufficient amount of the patients were available at follow up, 8 intention to treat analysis, 9: Comparability of treatment and 10: whether we considered the results valid and applicable.

